ABSTRACT OF THE DISCLOSURE

The present invention provides methods and compositions for generating novel nucleic acid molecules through targeted spliceosomal mediated RNA *trans*-splicing. The compositions of the invention include pre-*trans*-splicing molecules (PTMs) designed to interact with a target precursor messenger RNA molecule (target pre-mRNA) and mediate a *trans*-splicing reaction resulting in the generation of a novel chimeric RNA molecule (chimeric RNA). In particular, the PTMs of the present invention can be genetically engineered to interact with a specific target pre-mRNA expressed in cells of the skin so as to result in correction of genetic defects responsible for a variety of different skin disorders to encode a reporter molecule or protein that may have therapeutic benefit. The compositions of the invention further include recombinant vectors systems capable of expressing the PTMs of the invention and cells expressing said PTMs. The methods of the invention encompass contacting the PTMs of the invention with specific target pre-mRNA expressed within cells of the skin under conditions in which a portion of the PTM is *trans*-spliced to a portion of the target pre-mRNA to form a chimeric RNA molecule wherein the genetic defect in the specific gene has been corrected. The present invention is based on the successful *trans*-splicing of the collagen XVII pre-mRNA thereby establishing the usefulness of *trans*-splicing for correction of skin specific genetic defects. The methods and compositions of the present invention can be used in gene therapy for treatment of specific disorders of the skin, *i.e.*, genodermatoses, such as epidermal fragility disorders, keratinization disorders, hair disorders and pigmentation disorders as well as cancers of the skin.